wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy; or a pharmaceutically acceptable salt or hydrate or prodrug thereof.

52. (Amended) A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claims 45, 46, 47, 48 or 49, and a pharmaceutically acceptable excipient.

REMARKS

Claims 28-37, 40 and 42-54 are pending and stand ready for further action on the merits. Claims 28-33, 50, 51, 53 and 54 have been withdrawn from consideration as being drawn to non-elected subject matter. The above amendment has been made for further clarification. This is not a narrowing amendment, and no new matter has been added by way of the above-amendment.

Interview

Applicants note with appreciation that the Examiner conducted an interview with Applicants' representative on January 15, 2002. The Examiner was very helpful in clarifying the issues. During the interview, the Examiner began to appreciate the fact that the

proviso in the instant claims adequately distinguishes the presently claimed invention from the teachings of the cited references. Further details of this fact are given below.

Issues Under 35 U.S.C. §112, second paragraph

Claims 34-49 and 52 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully traverse the rejection.

Specifically, the Examiner objects to the last line of claims 34, 35, 40, 45, 46 and 49. Each of these claims recites ", pharmaceutically acceptable salt, hydrate, or prodrug thereof". In response, Applicants have amended the last two lines of each of these claims by replacing this phrase with "; or a pharmaceutically acceptable salt or hydrate or prodrug thereof". Accordingly, these claims include: 1) a compound; 2) a pharmaceutically acceptable salt of said compound; 3) a hydrate of said compound; or 4) a prodrug of said compound. In view of this amendment, Applicants respectfully submit that the claims adequately satisfy the requirements of 35 U.S.C. §112, second paragraph and withdrawal of the rejection is respectfully requested.

[I] Issues Under 35 U.S.C. §102 and §103

The following rejections are pending:

A. Claims 34-36 and 42-49 are rejected under 35 U.S.C. §102(b), and claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Goulding, U.S. 5,560,864;
B. Claims 34-36 and 45-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Kam Ming Chan et al., U.S. 4,594,465;
C. Claims 34-36 and 45-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Kurihara et al., U.S. 5,494,605;
D. Claims 34-36 and 42-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Reiffenrath et al., U.S. 5,487,845;
E. Claims 34-36 and 42-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Suzuki et al., U.S. 5,417,885;
F. Claims 34-36 and 42-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Gray et al., GB 2,227,742;
G. Claims 34-36 and 45-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Raynes et al., GB 2,198,743[1];
H. Claims 34-36 and 45-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Coates et al., GB 2,240,778;
I. Claims 34-35 and 45-49 are rejected under 35 U.S.C. §102(b), or, in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Gray et al., GB 2,200,912.

Applicants respectfully traverse each of the rejections.

[1] Based upon the Examiner's description of the rejection of Raynes et al., it appears that the Examiner has incorrectly identified the number of the UK patent application. The correct patent number for Raynes et al. is GB 2,198,743.

[IA] Advantages of the Present Invention

The present invention relates to a novel para-terphenyl compound, a process for producing the same, the use of said compound as a suppressor of the IgE production for treatment as an immunosuppressor and/or an anti-allergic agent. The inventive para-terphenyl compounds have the advantage of acting as a fundamental therapeutic agent for allergic diseases, and do not merely treat the symptoms of the allergic disease. The mechanism by which this occurs is by suppression of IgE antibody production.

The art has recognized certain compounds which act to suppress IgE antibody productions such as DSCG (intal) or Nedcromil sodium. However, these compounds also affect immunoglobulins other than IgE. Because immunoglobulins are necessary for phylaxis, the inventive compounds are superior to the prior art compounds in that the inventive compounds not only potent, but they have a high selectivity to IgE.

Applicants respectfully submit that the inventive compounds, process and methods of use are novel and non-obvious over the cited references. Now we turn to the individual claims and how each distinguishes from the cited references.

[IB] Claims 34-36 and 49

As was discussed in the interview, each of the cited documents disclose only compounds wherein all phenyl groups are substituted with hydrogen, halogen or cyano. Compounds wherein all of R2-13 are hydrogen, halogen or cyano are excluded in claims 34-36 and 49.

[IC] Claims 45-48

With respect to claims 45-48, the proviso excludes the compounds disclosed in the documents cited by the Examiner.

[ICi] U.S. 5,560,864

U.S. 5,560,864 discloses terphenyl derivatives wherein all phenyl groups are unsubstituted (e.g., IIIa 20, IIIa 21, IIIa 22, IIIa 23) and terphenyl derivatives wherein a phenyl group substituted with alkoxy is substituted with fluoro (e.g., a compound described at the bottom of Table in column 39 and 40).

The proviso excludes compounds wherein all of R2-R13 are hydrogen. The proviso also recites that when R6, R7, R8 and R9 are all simultaneously hydrogen, then all of R2, R3, R4, R5 and R12 are hydrogen.

Therefore, claims 45-48 are patentably distinct from U.S. 5,560,864, since U.S. 5,560,864 fails to teach or suggest the compounds of claims 45-48.

[ICii] U.S. 4,594,465, U.S. 5,494,605 and U.S. 5,417,885

U.S. 4,594,465, U.S. 5,494,605 and U.S. 5,417,885 disclose terphenyl derivatives wherein a central phenyl ring is substituted with hydrogen and halogen. Applicants respectfully submit that claims 45-48 are patentably distinct from these references, since compounds wherein one or more of R6, R7, R8 and R9 are halogen and the others are hydrogen are excluded.

[ICiii] U.S. 5,487,845

U.S. 5,487,845 discloses terphenyl derivatives wherein the substituent Q-Y is $OCHF_2$, OCF_3, C1, F or CF_3 (Example 19, 20, 41, 42, 63, 64, 86, 87, 117, 118, 189, 140, 163, 164, 194, 195).

Applicants respectfully submit that claims 45-48 are patentably distinct from this reference, since the substituents XY and R1 of a compound in claims 45-48 do not include these substituents.

[ICiv] GB 2 227 742

GB 2 227 742 discloses terphenyl derivatives wherein one of the side phenyl rings is substituted with alkyl (e.g., n-C_5H_{11}).

Applicants respectfully submit that claims 45-48 are patentably distinct from this reference, since the instant variable R1 does not include alkyl.

[ICv] GB 2 198 743

GB 2 198 743 discloses terphenyl derivatives wherein a central phenyl ring is substituted with hydrogen and halogen (e.g., Examples 1, 2, 3, 5, and 6) and terphenyl derivatives wherein one of the side phenyl rings is substituted with alkyl (e.g., n-C_9H_{19}).

Applicants respectfully submit that claims 45-48 are patentably distinct from this reference, since compounds wherein one or more of R6, R7, R8 and R9 are halogen and the others are hydrogen are excluded. In addition, the instant variable R1 does not include alkyl.

[ICvi] GB 2 240 778

GB 2 240 778 discloses terphenyl derivatives wherein one of the side phenyl rings is substituted with cycloalkyl (e.g.,

cyclohexyl) and the other is substituted with alkyl (e.g., C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, C_7H_{15}).

Applicants respectfully submit that claims 45-48 are patentably distinct from this reference, since compounds the instant variable R1 does not include cycloalkyl and alkyl. In addition, the instant variable X is -O-, -NH-, -NMe- or $-SO_2-$.

[ICvii] GB 2 200 912

GB 2 200 912 discloses terphenyl derivatives wherein a central phenyl ring is substituted with hydrogen and halogen (e.g., page 10, 12, 13, 14) and terphenyl derivatives wherein one of the side phenyl rings is substituted with alkyl (e.g., n-C_5H_{11}, n-C_9H_{19}).

Applicants respectfully submit that claims 45-48 are patentably distinct from this reference, since compounds wherein one or more of R6, R7, R8 and R9 are halogen and the others are hydrogen are excluded. In addition, the instant variable R1 does not include alkyl.

[ID] Anticipation

With regard to each of the cited references, the Examiner describes in the Office Action that compounds shown by general

formula include the present compounds by selecting the substituents which are generically suggested.

However, Applicants respectfully submit that the proviso of compound claims 34-36 and 45-49 excludes the generically suggested substituents. Even assuming *arguendo*, that they do generically suggest the substituents, this is an inappropriate analysis under Section 102. According to the MPEP 2132.02, a generic chemical formula will anticipate a claimed species covered by the formula only when the species can be "at once envisaged" from the formula. Based upon the details provided above regarding the provisos in the present claims, it is clear that the present claims do not contain compounds which would be "at once envisaged" by the skilled artisan and as such, the present claims 34-36 and 45-49 are not anticipated.

[IE] Obviousness

Applicants respectfully submit that the proviso of compound claims 34-36 and 45-49 excludes the generically suggested substituents. As the MPEP directs, all the claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of obviousness. See MPEP § 2143.03.

[IEi] Homologs

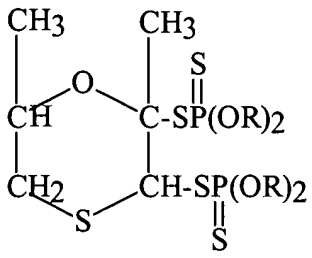
During the interview, the Examiner indicated that the present claims, even though they do not contain compounds which are anticipated by the prior art, may contain compounds which are homologs of the prior art compounds. A homolog is defined as two compounds which differ by a methylene group (CH2). In other words, the Examiner indicated that it would be obvious to modify the prior art compounds by placing a methyl group on one of the terphenyl rings of the prior art compounds.

Applicants respectfully submit that in order for the Examiner to properly make a *prima facie* case of obviousness based on homologs, it is necessary that the skilled artisan should be able to predict the properties of the fictitious compounds containing the added methylene group. In other words, the skilled artisan would need to be able to reasonably predict that even after adding a methyl group to one of the phenyls of the terphenyl group in the prior art compounds, that the prior art compounds would still retain its liquid crystalline properties.

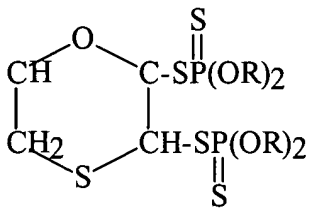
In support of the Examiner's position, the Examiner cites two cases, *In re Wood* 199 USPQ 137 (CCPA 1978) and *In re Lohr* 137 USPQ 548 (CCPA 1963). Applicants respectfully submit that the facts of

the present case are distinct from those of *Lohr* and *Wood*, such that these cases do not control.

In Lohr, the claims in the application included the following compound:

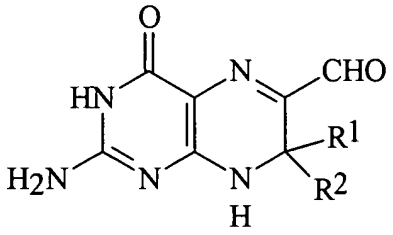


The cited prior art reference taught the following compound:



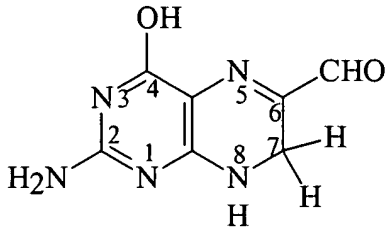
The court found that it would be obvious to add the two methyl groups to the 2- and 6- positions of the compound of the prior art with the expectation that the compound would be useful as a pesticide.

With regard to *Wood*, the application claim included the following compound:



(wherein R1 and R2 may be each a methyl group).

The prior art cited against Wood taught the following compound:



The appellate court found that it would be obvious to modify the prior art compound by adding two methyl groups at the 7-position with the expectation that these compounds would have antimicrobial activity.

Applicants note that there are two distinctions which have such weight as to make *Lohr* and *Wood* not control the present case.

(1) The ring in question where the modification takes place are heterocyclic rings which are non-aromatic. This is in distinction to the present situation where the modification is to take place on a **non**heterocyclic aromatic ring.

(2) The compounds in the prior art cited against the application of *Lohr* were useful as pesticides and the prior art compounds cited against the application in *Wood* were useful as anti-microbial agents. Each of these areas of use have a relatively higher degree of predictability when compared to the liquid crystalline materials taught in the references cited against the present claims.

Regarding **(1)**, Applicants respectfully submit that the modification of adding a methyl group to a phenyl ring of a terphenyl group, results in an unpredictable change in properties. This can be seen in the following table:

Compound	**Melting Point (°C)**
Benzene	5.5
Methylbenzene (toluene)	-93
Ethylbenzene	-95
Propylbenzene	-99

As can be seen from the above table, there is a huge change in the melting point when adding a methyl group to a benzene ring. However, once the methyl group has been added to the benzene ring, the addition of further methylene groups results in a modest change

to the melting point. The change in melting points going from benzene to toluene would not be predictable, but the change resulting from further additions of methylene groups to toluene would be predictable by the skilled artisan.

Regarding **(2)**, Applicants respectfully submit that the prior art has recognized that small structural changes to the terphenyl rings could result in a compound that does not show liquid crystalline properties.

As a generalized teaching of the structural requirements for compounds to show liquid crystal properties, Applicants have attached hereto the teachings of Collings (P.J. Collings, Kirk-Othmer Encyclopedia of Chemical Technology, 4^{th} Edition, Vol. 15, 1995, pages 372, 373 and 392). Collings teaches that liquid crystals differ from either solids or liquids, in that the molecules are capable of diffusing in a manner like liquids, however, they still retain a small degree of long range orientational and sometimes positional order thereby resulting in an anisotropic phase. These liquid crystal phases are thermodynamically stable for temperature ranges between the solid and the isotropic liquid phases.

Collings states:

> Just because a molecule is long, narrow, and meets the requirement of geometric anisotropy does not ensure

> that it will have a liquid crystal phase. For example, the K-paraffins and homologues of acetic acid are not liquid crystalline. The forces of attraction between these molecules are not sufficiently strong for an ordered, parallel arrangement to be retained after the melting of the solid. In addition, steric effects which promote parallel alignment are not strong in molecules which are extremely flexible and thus deviate significantly from an elongated shape.

In summary, Collings teaches that there is a delicate balance between the intermolecular forces for the compounds to have a liquid crystal property.

As evidence of this fact, the Examiner's attention is directed to the cited references which only teach that the phenyl rings of the terphenyl group are substituted by a hydrogen, fluorine or a cyano group. Clearly this is not an accident, since the inventors and assignees of each of the cited patents are, for the most part, unrelated. The inventors of each of the cited patents are aware that substituents which are other than H, F or CN, for example, a methyl group could deleteriously affect the liquid crystalline properties of the terphenyl compounds.

In view of the foregoing, Applicants respectfully submit that the skilled artisan would not find it obvious to modify the terphenyl groups of the cited prior art references to have a methyl group attached thereto with the expectation that the final compounds would have liquid crystalline effects. Accordingly,

Applicants respectfully request that the rejections under 35 U.S.C. §102 and §103 are withdrawn.

Conclusion

In view of the above amendments and comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

Applicants have attached hereto a marked up version of the claims to show the changes made for the Examiner's convenience.

If the Examiner has any questions concerning this application, he is requested to contact the Garth M. Dahlen, Ph.D. (#43,575) at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Marc S. Weiner, #32,181

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(703) 205-8000

MSW/GMD/gh
0032-0248P
Attachment: Version with Markings to Show Changes Made
Collings Article

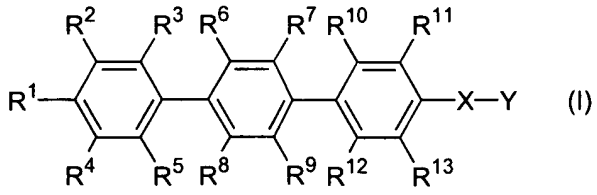
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 38, 39 and 41 have been cancelled.

The claims have been amended as follows:

34. (Amended) A compound of the formula (I):



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$,$-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl and which may optionally be substituted,

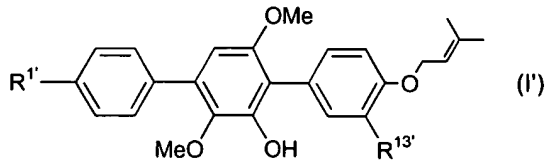
excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen, compounds wherein all of R^6,

R^7, R^8 and R^9 are halogen and compounds wherein all of R^2-R^{13} are hydrogen, halogen or cyano,

provided that R^1 is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, or R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are all simultaneously hydrogen,

and further provided that R^1 is not methyl or acetyloxy, R^{13} is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl, or -X-Y is not methoxy when at least one of R^6, R^7, R^8 and R^9 is a substituent other than hydrogen,

and excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy[,]; or a

pharmaceutically acceptable salt[,] or hydrate or prodrug thereof.

35. (Amended) The compound claimed in claim 34 wherein R^1 is hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio,

optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyloxy, lower alkylsulfonyl, formyl, optionally substituted amino, lower alkylsulfinyl, acyloxy, nitro, cyano, optionally substituted sulfamoyl or heterocyclyl,

R^2 is hydrogen, hydroxy, halogen, optionally substituted lower alkyl or optionally substituted lower alkylsulfonyloxy,

R^3 is hydrogen, hydroxy, halogen or optionally substituted lower alkoxy,

R^4 is hydrogen, optionally substituted lower alkyl, halogen, optionally substituted lower alkoxy, nitro or optionally substituted amino,

R^5 is hydrogen, optionally substituted lower alkoxy, lower alkoxycarbonyl or carboxy,

R^6 is hydrogen, halogen, optionally substituted lower alkyl, carboxy, lower alkoxycarbonyl, nitro, formyl, amino or lower alkylsulfonyloxy,

R^7 and R^8 are each independently hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, formyl or optionally substituted amino,

R^9 is hydrogen, hydroxy, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkoxycarbonyl,

optionally substituted lower alkylsulfonyloxy, formyl, optionally substituted carbamoyl or optionally substituted amino,

R^{10} is hydrogen or lower alkoxy,

R^{11} is hydrogen, halogen, optionally substituted lower alkyl, carboxy, lower alkoxycarbonyl, optionally substituted lower alkylsulfonyloxy, formyl, nitro or amino,

R^{12} is hydrogen,

R^{13} is hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted acyloxy, optionally substituted lower alkylsulfonyloxy, formyl, nitro or optionally substituted amino,

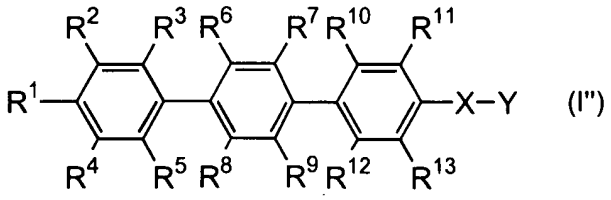
Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl or optionally substituted cycloalkenyl and Y may be optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

and R^1 and R^2, R^1 and R^4, R^8 and R^9, R^{11} and -X-Y, or R^1 and -X-Y taken together may form a 5- or 6-membered ring which contains one or more of O or NR^{15} wherein R^{15} is the same as defined in claim 34 and which may optionally be substituted[,]; or a

pharmaceutically acceptable salt[,] or hydrate or prodrug thereof.

37. (Amended) [The] A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claim 34 or 35, and a pharmaceutically acceptable excipient.

40. (Amended) An immunosuppressor comprising a compound of the formula (I''):



(I'')

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7,R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl optionally substituted, lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally

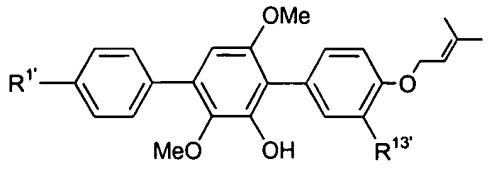
substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, $-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or optionally substituted arylsulfonyl and which may optionally be substituted,

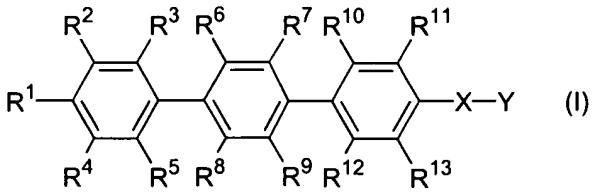
excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy[,]; or a pharmaceutically acceptable salt[,] or hydrate or prodrug thereof, and a pharmaceutically acceptable excipient.

45. (Amended) A compound of the formula (I):



(I)

wherein R^1 is hydrogen, halogen, optionally substituted lower alkenyloxy, optionally substituted lower alkylsulfonyloxy, optionally substituted amino or optionally substituted sulfamoyl,

R^2 is hydrogen, halogen or lower alkyl having 1 to 3 carbon atoms,

R^3 is hydrogen or halogen,

R^4 is hydrogen, lower alkyl, lower alkoxy or halogen,

R^5 is hydrogen, lower alkoxycarbonyl or carboxy,

R^6 is hydrogen, lower alkyl or halogen,

R^7 is hydrogen, lower alkyl or lower alkoxy,

R^8 is hydrogen, lower alkyl or lower alkoxy,

R^9 is hydrogen, hydroxy, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyloxy, formyl, optionally substituted carbamoyl or optionally substituted amino,

R^{10} is hydrogen,

R^{11} is hydrogen or halogen,

R^{12} is hydrogen,

R^{13} is hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted acyloxy, optionally substituted lower alkylsulfonyloxy, formyl or optionally substituted amino,

X is -0-, -NH-, -NMe- or $-SO_2-$,

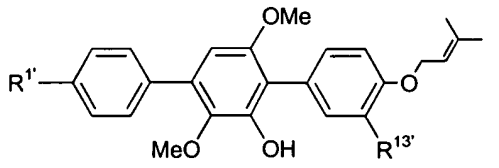
Y is lower alkyl optionally substituted with lower alkoxycarbonyl, aryl, lower alkylaryl, halogenoaryl, lower alkoxyaryl, heterocyclyl or acyl; or lower alkenyl optionally substituted with hydroxy, halogen or aryl,

and R^1 and R^4 or R^8 and R^9 taken together may form a 5- or 6-membered ring which contains one or more of 0,

excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen and compounds wherein all of R^2-R^{13} are hydrogen,

provided that R^1 is not hydrogen or fluorine, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, or R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are an simultaneously hydrogen,

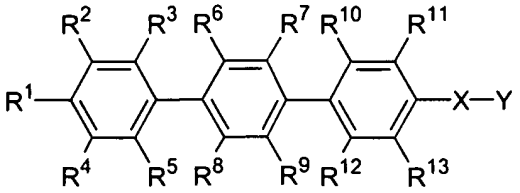
and further provided that R^{13} is not hydrogen or -X-Y is not methoxy when at least one of R^6, R^7, R^8 and R^9 is a substituent other than hydrogen, and excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$, is hydrogen or hydroxy and $R^{13'}$is hydroxy or methoxy[,]; or a pharmaceutically acceptable salt[,] or hydrate or prodrug thereof.

46. (Amended) A compound of the formula (I):



(I)

wherein R^1 is hydrogen, hydroxy, halogen, optionally substituted lower alkoxy, optionally substituted alkenyloxy, optionally substituted lower alkylsulfonyloxy, optionally substituted amino or optionally substituted sulfamoyl,

R^2 is hydrogen, halogen or lower alkyl having 1 to 3 carbon atoms,

R^3 is hydrogen or halogen,

R^4 is hydrogen, lower alkyl, lower alkoxy or halogen,

R^5 is hydrogen, lower alkoxycarbonyl or carboxy,

R^6 is hydrogen, lower alkyl or halogen,

R^7 is hydrogen, lower alkyl or lower alkoxy,

R^8 is hydrogen, lower alkyl or lower alkoxy,

R^9 is hydrogen, hydroxy, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyloxy,

formyl, optionally substituted carbamoyl or optionally substituted amino,

R^{10} is hydrogen,

R^{11} is hydrogen or halogen,

R^{12} is hydrogen,

R^{13} is hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted acyloxy, optionally substituted lower alkylsulfonyloxy, formyl or optionally substituted amino,

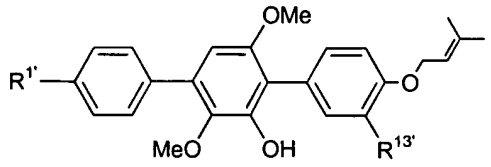
X is -O-, -NH-, -NMe- or $-SO_2-$,

Y is lower alkyl optionally substituted with aryl; or lower alkenyl,

and R^1 and R^4 or R^8 and R^9 taken together may form a 5- or 6-membered ring which contains one or more of O,

excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen and compounds wherein all of R^2-R^{13} are hydrogen, provided that R^1 is not hydrogen, fluorine or optionally substituted lower alkoxy, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, or R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are all simultaneously hydrogen, and further provided that R^{13} is not hydrogen or -X-Y is not methoxy when at least one of

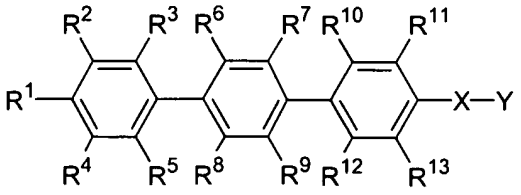
R^6, R^7, R^8 and R^9 is a substituent other than hydrogen, and excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy[,]; or a pharmaceutically acceptable salt[,] or hydrate or prodrug thereof.

49. (Amended) A compound of the formula (I):



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower

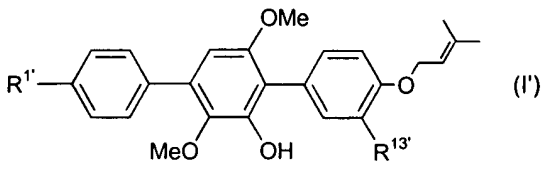
alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$,$-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or $-S(O)_p-$ wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may be optionally substituted lower alkoxy when X is $-CH_2-$ and may be optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$, R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen,

optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl and which may optionally be substituted, excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen, compounds wherein all of R^6, R^7, R^8 and R^9 are halogen and compounds wherein all of R^2-R^{13} are hydrogen, halogen or cyano, provided that R^1 is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, and R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are all simultaneously hydrogen, and further provided that R^1 is not methyl or acetyloxy, R^{13} is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl, and -X-Y is not methoxy when at least one of R^6, R^7, R^8 and R^9 is a substituent other than hydrogen,

and excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy[,]; or a pharmaceutically acceptable salt[,] or hydrate or prodrug thereof.

52. (Amended) A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claims 45, 46, 47, 48 or 49 and a pharmaceutically acceptable excipient.

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FOURTH EDITION

VOLUME 15

LASERS
TO
MASS SPECTROMETRY



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Lithium and
Compounc
Lubrication a

reducing the value of the butanes as blending stocks. However, normal butane can be used as feedstock for production of isobutylene, a key ingredient of ether blendstocks, such as methyl *tert*-butyl ether [*1634-04-4*] (MTBE) for motor gasoline. Shifts in U.S. use patterns can be seen in Table 3.

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LIQUID CRYSTALLINE MATERIALS

Liquid crystals represent a state of matter with physical properties normally associated with both solids and liquids. Liquid crystals are fluid in that the molecules are free to diffuse about, endowing the substance with the flow properties of a fluid. As the molecules diffuse, however, a small degree of long-range orientational and sometimes positional order is maintained, causing the sub-

stance to be anisotropic as is typical of solids. Therefore, liquid crystals are anisotropic fluids and thus a fourth phase of matter. There are many liquid crystal phases, each exhibiting different forms of orientational and positional order, but in most cases these phases are thermodynamically stable for temperature ranges between the solid and isotropic liquid phases. Liquid crystallinity is also referred to as mesomorphism.

Many thousands of organic substances, some rigid-rod polymers, and other macromolecules exhibit liquid crystallinity. The general common molecular feature is either an elongated or flattened, somewhat inflexible molecular framework, which is usually depicted as either a cigar- or disk-shaped entity. Certain macromolecules and some amphiphilic molecules, containing both hydrophilic and oliophilic moieties, adopt liquid crystalline structures in solution. The orientational and positional order in a liquid crystal phase is only partial, with the intermolecular forces striking a very delicate balance involving both attractive and repulsive interactions. As a result, liquid crystals are extraordinarily sensitive to external perturbations, eg, temperature, pressure, electric and magnetic fields, shearing stress, or foreign vapors. For this reason, liquid crystals are used to design practical devices to either monitor ambient changes of various kinds or to transduce an environmental fluctuation into a useful electrical or optical output.

Besides being used in the scientific study of cooperative phenomena and complex fluid phases, liquid crystalline phenomena have received a good deal of attention due to the possibility of practical applications. Liquid crystals are widely used in electrooptic displays, eg, digital watches, calculators, portable computers, televisions, and electronic instrumentation. Other applications include radiation and pressure sensors, optical switches and shutters, and thermography. The liquid crystalline structures formed by amphiphilic molecules form the basis for emulsions and are studied thoroughly by researchers in the food, drug, and oil industries. Polymers that form an anisotropic fluid phase are important in the fabrication of lightweight, ultrahigh strength, and temperature-resistant fibers, and are beginning to be used in electrooptic displays. Liquid crystals also appear to play an important role in the structure and biochemical function of living tissue, where the characteristic combination of order and flow mobility is particularly suited to life processes. Certain disease states, eg, atherosclerosis, sickle cell anemia, or cancer, may be associated with physical changes in the liquid crystalline order within biological structures.

Orientational and Positional Order in Fluids

Conventionally, matter exists in one of three distinct states of aggregation: the solid state, where constituent molecules or atoms execute small vibrations about firmly fixed lattice positions but cannot rotate or translate; the liquid state, characterized by hindered rotation and translation but no long-range order; and the gaseous state, where particles move freely through the entire volume of the container, with almost no constraint to rotation or translation. The melting of normal solids involves the abrupt collapse of the overall positional and orientational order of the lattice and marks the onset of hindered rotation and translation of the molecules. Short-range correlations of the position and

An exception to the rule that lowering the temperature causes transitions to phases with increased order sometimes occurs for polar compounds which form the smectic A_d phase. Decreasing the temperature causes a transition from nematic to smectic A_d, but a further lowering of the temperature produces a transition back to the nematic phase (called the reentrant nematic phase) (22). The reason for this is the unfavorable packing of the molecules in the smectic A_d phase due to overlap of the molecules in the center of the layers. As the temperature is lowered, the steric interactions overpower the attractive forces, causing the molecules to pack much more favorably in the nematic phase. The reentrant nematic phase can also be produced from the smectic A_d phase by increasing the pressure (23).

Electric or magnetic fields also may induce mesomorphic phase transitions. If a chiral nematic liquid crystal is composed of molecules with positive dielectric or diamagnetic susceptibility, an applied field tends to align the director along the field direction. At sufficiently high field strengths, a transition to the nematic phase can occur as the helical structure is unwound. This chiral nematic to nematic transition is continuous and occurs at a critical field strength inversely proportional to the pitch of the chiral nematic in zero field. For a thermotropic chiral nematic with a pitch in the micrometer range, the critical magnetic field is several teslas and the critical electric field can be anywhere between 1 and 5 million volts per meter. For certain lyotropic polymer solutions with a longer pitch, the critical field is one to two orders of magnitude lower (24).

Synthesis

Just because a molecule is long, narrow, and meets the requirement of geometric anisotropy does not ensure that it will have a liquid crystal phase. For example, the *n*-paraffins and homologues of acetic acid are not liquid crystalline. The forces of attraction between these molecules are not sufficiently strong for an ordered, parallel arrangement to be retained after the melting of the solid. In addition, steric effects which promote parallel alignment are not strong in molecules which are extremely flexible and thus deviate significantly from an elongated shape. The particular phase structure that occurs in a compound, ie, smectic, nematic, or chiral nematic, not only depends on the molecular shape but is intimately connected with the strength and position of the polar or polarizable groups within the molecule, the overall polarizability of the molecule, and the presence of chiral centers.

Molecular interactions that lead to attraction include dipole–dipole interactions, dipole-induced dipole interactions, dispersion forces, and hydrogen bonding. Dispersion forces alone, at least in simple aliphatic flexible compounds, apparently are inadequate to achieve the degree of molecular order necessary for liquid crystallinity, eg, the straight-chain paraffins which melt to form normal liquids.

In order for dipole–dipole and dipole-induced dipole interactions to be effective, the molecule must contain polar groups and/or be highly polarizable. Ease of electronic distortion is favored by the presence of aromatic groups and double or triple bonds. These groups frequently are found in the molecular structure